Claims

1. A fusion protein with the formula :

(a) X-Y, or

(b) Y-X,

wherein X represents a first immunoregulatory polypeptide;

Y represents a second immunoregulatory polypeptide; and

X is different from Y.

2. The fusion protein of claim 1, wherein said X and Y each represents a cytokine.

3. The fusion protein of claim 2, wherein X represents a cytokine capable of enhancing a nonspecific immune response.

4. The fusion protein of claim 3, wherein said nonspecific immune response is mediated by one or more of the effector cells selected from the group consisting of macrophages, dendritic cells, NK cells and NKT cells.

5. The fusion protein of any one of claims 2 to 4, wherein Y represents a cytokine capable of enhancing a specific immunity.

6. The fusion protein of claim 5, wherein said specific immunity is mediated by the effector cells B and/or T lymphocytes.

7. The fusion protein of any one of claim 2 to 6, wherein X and Y independently are IL-2, IL-7, IL-15, IL-18, IL-21, IL-27, IL-31 or IFNg.

8. The fusion protein of claim 7, wherein :

(a) X is IL-2 and Y is selected from the group consisting of IL-7, IL-15, IL-18, IL-21, IL-27, IL-31 and IFNg;

(b) X is IL-12 and Y is selected from the group consisting of IL-15, IL-18 and IL-21;

(c) X is IL-15 and Y is IL-7, IL-18 or IL-21; or

(d) X is IL-18 and Y is IL-21.

9. The fusion protein of claim 8, which :

(a) has the formula Y-X, wherein X is IL-2 and Y is IL-7;

(b) has the formula X-Y or Y-X, wherein X is IL-2 and Y is IL-15 ;

(c) has the formula X-Y, wherein X is IL-2 and Y is IL-18 ;

(d) has the formula Y-X, wherein X is IL-2 and Y is IL-21 ;

(e) has the formula Y-X, wherein X is IL-2 and Y is IFN-g ;

(f) has the formula X-Y, wherein X is IL-15 and Y is IL-7;

(g) has the formula X-Y or Y-X, wherein X is IL-15 and Y is IL-18 ;

(h) has the formula X-Y or Y-X, wherein X is IL-15 and Y is IL-21 ; and

(i) has the formula X-Y or Y-X, wherein X is IL-18 and Y is IL-21.

10. The fusion protein of any one of claims 7 to 9, wherein said IL-2 is an IL-2 variant which exhibits a reduced cytotoxicity as compared to the corresponding native IL-2.

11. The fusion protein of claim 10, wherein said IL-2 variant is selected from the group consisiting of :

(a) the variant F42K having the phenyl alanine residue in position 42 of the native IL-2 substituted by a lysine residue;

(b) the variant R38A having the arginine residue in position 38 of the native IL-2 substituted by an alanine residue;

(c) the variant D20I having the aspartic acid residue in position 20 of the native IL-2 substituted by an isoleucine residue;

(d) the variant N88G having the asparagine residue in position 88 of the native IL-2 substituted by a glycine residue;

(e) the variant N88R having the asparagine residue in position 88 of the native IL-2 substituted by an arginine residue;

(f) the variant Q126M having the glutamine residue in position 126 of the native IL-2 substituted by a methionine residue; and

(g) any combination of (a) to (f).

12. The fusion protein of any one of claims 7 to 11, wherein said IL-18 is an IL-18 variant.

13. The fusion protein of claim 12, wherein said IL-18 variant is the variant K89A having the lysine residue in position 89 of the corresponding native IL-18 substituted by an alanine residue.

14. The fusion protein of any one of claims 7 to 13, wherein said IL-18 is a proIL-18.

15. The fusion protein of any one of claims 7 to 14, wherein said fusion protein comprises an amino acid sequence which is at least 70% homologous to all or part of any of the amino acid sequences recited in SEQ ID NO: 1-19.

16. The fusion protein of claim 15, wherein said fusion protein comprises an amino acid sequence which is 100% homologous to all or part of any of the amino acid sequences recited in SEQ ID NO: 1-19.

17. A nucleic acid molecule encoding the fusion protein of any one of claims 1 to 16.

18. A vector containing the nucleic acid molecule of claim 17.

19. The vector of claim 18, wherein said vector is derived from one or more bacterial plasmids, bacteriophages, yeast episomes, artificial chromosomes, or from viruses selected from the group consisting of baculoviruses, papovaviruses, herpes viruses, adenoviruses, adenovirus-associated viruses (AAV), poxviruses, foamy viruses, and retroviruses.

20. The vector of claim 19, wherein said vector is an adenoviral vector.

21. The vector of claim 20, wherein said vector is an E1- and E3-deleted replication-defective adenoviral vector comprising the nucleic acid molecule according to claim 17 inserted in replacement of the E1 region and placed under the control of the CMV promoter.

22. The vector of any one of claims 18 to 21, wherein said vector further comprises one or more transgenes encoding (i) a tumor proliferation inhibitor and/or (ii) at least one antigen against which an immune response is desired.

23. The vector of claim 22, wherein said tumor proliferation inhibitor is a fusion protein which encodes a two domain enzyme possessing both CDase and UPRTase activities.

24. The vector of claim 22, wherein said specific antigen is a HPV antigen selected from the group consisting of E5, E6, E7, L1, and L2 either individually or in combination.

25. The vector of claim 24, wherein said HPV antigen is a membrane-anchored form of a non-oncogenic variant of the early HPV-16 E6 and/or E7 antigen.

26. An infectious viral particle comprising a nucleic acid molecule according to claim 17 or a vector according to any of claims 18 to 25.

27. A process for producing an infectious viral particle according to claim 26, comprising the steps of:

(a) introducing the viral vector of any one of claims 18 to 25 into a suitable cell line,

(b) culturing said cell line under suitable conditions so as to allow the production of said infectious viral particle, and

(c) recovering the produced infectious viral particle from the culture of said cell line, and

(d) optionally purifying said recovered infectious viral particle.

28. A host cell comprising the nucleic acid molecule according to claim 17 or the vector according to any one of claims 18 to 25 or the infectious viral particle of claim 26.

29. A method for producing the fusion protein according to any one of claims 1 to 16, comprising introducing a vector according to any one of claims 18 to 25 or an infectious viral particle according to claim 26 into a suitable host cell to produce a transfected or infected host cell, culturing *in-vitro* said transfected or infected host cell under conditions suitable for growth of the host cell, and thereafter recovering said fusion protein from said culture, and optionally, purifying said recovered fusion protein.

30. A pharmaceutical composition comprising an effective amount of the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25,

the infectious viral particle according to claim 26, the host cell according to claim 28 or any combination thereof and optionally a pharmaceutically acceptable vehicle.

31. Use of the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25, the infectious viral particle according to claim 26, the host cell according to claim 28 or the composition of claim 30, for the preparation of a drug intended for treating or preventing cancer or an infectious disease.

32. The use according to claim 31, wherein said composition is administered into or in close proximity to a solid tumor.

33. The use according to claim 31 or 32, wherein said fusion protein, said vector, said infectious viral particle, said host cell or said composition is administered in combination with one or more transgenes or transgene products.

34. A method for the treatment of a human or animal organism, comprising administering to said organism a therapeutically effective amount of the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25, the infectious viral particle according to claim 26, the host cell according to claim 28 or the composition of claim 30.

35. A method for enhancing an immune response in an animal or human organism comprising introducing into said organism the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25, the infectious viral particle according to claim 26, the host cell according to claim 28 or the composition of claim 30, so as to enhance said immune response.

36. Use of the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25, the infectious viral particle according to claim 26, the host cell according to claim 28 or the composition of claim 30, for the preparation of a drug intended for the purpose of activating maturation of dendritic cells in an animal or human organism.

37. The use according to claim 36, wherein the fusion protein has the formula X-Y, wherein X is IL-2 and Y is IL-18 or the formula Y-X, wherein X is IL-2 and Y is IL-7.

38. Use of the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25, the infectious viral particle according to claim 26, the host cell according to claim 28 or the composition of claim 30, for the preparation of a drug intended for the purpose of activating NKT cells in an animal or human organism.

39. The use according to claim 38, wherein the fusion protein has the formula X-Y, wherein X is IL-2 and Y is IL-18.

40. Use of the fusion protein according to any one of claims 1 to 16, the vector according to any one of claims 18 to 25, the infectious viral particle according to claim 26, the host cell according to claim 28 or the composition of claim 30, for the preparation of a drug providing lower cytotoxicity upon administration in an animal or human organism as compared to the cytotoxicity observed upon administration of the individual X and/or Y entities.

41. The use according to claim 40, wherein the fusion protein has the formula X-Y, wherein X is IL-2 and Y is IL-18, or the formula Y-X, wherein X is IL-2 and Y is IL-7.